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Maintenance of metabolism during intensive patient care

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The study of metabolism during intensive patient care

The maintenance of metabolism during severe illnesses may be defined as the provision of the observed or predicted need for calories, water, electrolyte, nitrogen and other essential nutrients so as to preserve normal metabolic processes and prevent significant change in the acid–base state.

Nature and size of the problem

In an illness of moderate severity or short duration neglect of nutrition may not be serious, but this cannot be said of the serious illnesses which need Intensive Therapy, especially when complicated by trauma, sepsis or abnormal electrolyte loss. In these situations neglect of metabolic care may prove fatal, or predispose to further complications and protracted hospital stay. In the past it has been held that the metabolic response to illness or trauma was an effect of the disease state and was both inevitable and irreversible. 'This tissue breakdown in response to injury or surgery is almost certainly due to an increased secretion of cortical hormones by the adrenal glands. . . . It is not possible to prevent this loss of tissue by dietary measures and, in so far as it seems to be a physiological response, there is little justification for attempting to do so' (Davidson & Passmore, 1966). This view probably originated from the early observations on the metabolic response to trauma which revealed increased nitrogen losses in the urine (Cuthbertson, 1930) which could not be prevented by eating a diet rich in first-class protein (Cuthbertson, 1942). If measures are taken to provide food over and above the patient's spontaneous appetite, it is possible to reverse the negative nitrogen balance which is a feature of the metabolic response to surgery (Riegel *et al.*, 1947) or burns (Meyer, Hirschfeld & Abbott, 1947).

The present studies were largely conducted in an Intensive Care Unit on patients with various acute medical illnesses, especially respiratory failure, pulmonary infection and accidental or surgical trauma. It was necessary to devise a system of metabolic care which would help in the day-to-day management of patients with serious illnesses, provide optimum nutrition via the naso-gastric or intravenous routes, and maintain the acid–base state as closely as possible to normal.

Methods for the study of metabolism

Since Claude Bernard first pointed to the constant nature of the 'milieu intérieur' (Bernard, 1859) medical science has striven to apply this concept to the problems of metabolic care. Before any advance in therapeutics was possible, however, it was necessary to know as much as possible about the extracellular and cellular compartments; their chemical composition and the qualitative and quantitative changes in disease. Several methods for obtaining this information have been developed. Post-mortem or post-surgical material may be examined (Forbes & Lewis, 1956) but this method clearly has no direct application to therapeutics. A similar anatomical method, but with equal disadvantages, uses small tissue samples, such as skeletal muscle (Mudge & Vislocky, 1949; Ariel, 1952; Cooke *et al.*, 1952; Talso, Spafford & Blaw, 1953; Barnes, Gordon & Cope, 1957; Litchfield & Gaddie, 1958; Bergstrom, 1962).

Biochemical investigations employing non-radioactive dilution methods have been used to assess the body composition (Crooke & Morris, 1942; Cruickshank & Whitfield, 1945; Schwartz, Schachter & Freinkel, 1949; Courtice & Guntar, 1949; Edwards & White, 1960) but the results show variations according to the materials used. Thus although sucrose, inulin and thiosulphate may all be used to measure the extracellular fluid volume, the three results all vary to a significant extent because of differences in distribution (Ikkos, 1955). Furthermore, the results by some methods, such as sucrose space, may vary in the same healthy individual throughout 24 hr (Peterson, O'Toole & Kirkendahl, 1959).

With the introduction of reliable flame photometry it became possible to measure accurately the electrolyte contents of the serum and some of the body fluid compartments; normal values were then available for diagnosis. Interpretation of serum electrolyte values, however, requires an appreciation of the sometimes gross errors in their measurement (Thomson & Jones, 1965) and of the biological variables which affect the final common denominator of concentration (Scribner & Burnell, 1956; Wynn, 1957).

The introduction of isotope methods facilitated

the study of the body compartments and supplied a means of measuring the exchanges of water and electrolyte. Some of the compartments now measurable with isotopes are given in Table 1.

TABLE 1
Metabolic applications of isotope measurements

Measurement	References
Blood volume	Reeve & Veall (1949) Brady *et al.* (1953) Reilly *et al.* (1954)
Extracellular fluid volume	Reid *et al.* (1956) Nicholson & Zilva (1960) Staffurth & Birchall (1960)
Total body water	Moore (1946) Schloerb *et al.* (1950) Edelman & Moore (1951) Edelman *et al.* (1952) Prentice *et al.* (1952) Farber & Soberman (1956) Cooper *et al.* (1958)
Exchangeable sodium	Forbes & Perley (1951) Edelman *et al.* (1954) Farber & Soberman (1956) Cooper *et al.* (1958) Edelman *et al.* (1958) Adesman *et al.* (1960)
Exchangeable potassium	Corsa *et al.* (1950) Aikawa *et al.* (1952) Edelman *et al.* (1954) Wilson *et al.* (1954) Adesman *et al.* (1960)
Multiple simultaneous measurement of body electrolytes	James *et al.* (1954) Burrows *et al.* (1955) Cooper *et al.* (1958) McMurrey *et al.* (1958) Crooks, Bluhm & Muldowney (1959) Adesman *et al.* (1960) Shires, Williams & Brown (1960)

Rationale of external metabolic balance

The concept of external metabolic balance is based on the fact that for many essential factors, such as nitrogen and electrolyte, there is an equilibrium between intake and excretion. If all sources of intake and excretion, secretion or metabolism of a given factor are included and there is no change in the size of the body pool for that factor, then intake normally equals output. It is fortunate that the intake is normally oral or via the intravenous route, and the predominant excretion of many of the important variables is in the urine. Thus if a patient receives a constant diet by mouth, naso-gastric tube or vein, analysis of the urine can provide a continuous picture of the balance of each factor, a positive balance meaning that the intake of a factor exceeds the excretion, and a negative balance the converse.

Since the losses of nitrogen and electrolyte in the stool and from the skin are normally small, the application of corrections for these losses enables a balance picture to be obtained from urinalysis alone, although fluid balance is less accurate because of large variations in the insensible water loss (Blainey & Squire, 1960).

Several facts require appreciation before the method is used clinically. The dietary intake must either be of known constant value, or duplicate samples of all foods must be analysed, since the composition of normal foods is so variable (Pearson, Bahkov & Reiss, 1955). For this reason emulsified ward meals for naso-gastric tube feeding are useless for metabolic balance studies unless samples are analysed. The use of a synthetic tube feed of known

TABLE 2
Applications of external balance measurements

Clinical study	References
Malnutrition	Winkler *et al.* (1944) Howard *et al.* (1946) Beattie, Herbert & Bell (1948) Werner (1948) Keys *et al.* (1950) Forsyth *et al.* (1955)
Water, calorie and electrolyte depletion	Black, McCance & Young (1944) Winkler *et al.* (1944) McCance (1945) Darrow (1946) Engel & Jaeger (1954)
Normal variation	Stanbury & Thomson (1951)
Tube-fed diets	Lowe (1953) Pareira *et al.* (1954) Jones & Sechiari (1963) Masterton, Dudley & McRae (1963) Peaston (1966c)
Metabolic response to surgery	CoTui *et al.* (1944) Riegel *et al.* (1947) Werner *et al.* (1949) Brain & Stammers (1951) Elman & Weichselbaum (1952) Moore & Ball (1952) Le Quesne & Lewis (1953) Strickler, Rice & Taylor (1956) Holden *et al.* (1957) Timoner, Riddell & Carr (1959)
Post-traumatic metabolism	Cuthbertson (1930) Cuthbertson (1934) Cuthbertson (1942) Howard *et al.* (1944a) Howard *et al.* (1944b) Howard (1945) Peters (1948) Sachar, Walker & Whittico (1950) Cuthbertson (1954) Flear & Clarke (1955) Forsyth *et al.* (1955) Kinney (1959)
Congestive cardiac failure	Sinclair-Smith *et al.* (1949) Iseri, Boyle & Myers (1950)

and constant composition allows balance measurements to be made on urinalysis alone, and so halves the work involved and removes the error inherent in the analysis of food samples. The validity of using this method for external metabolic balance studies has been confirmed (Table 2).

in sweat are small, but in stool are a significant proportion of the total nitrogen excretion. With solid diets faecal nitrogen does not vary with the protein intake (Schamberg *et al.*, 1913; Martin & Robison, 1922; Mitchell, 1926; Smith, 1926). Faecal nitrogen is more closely related to the amount of

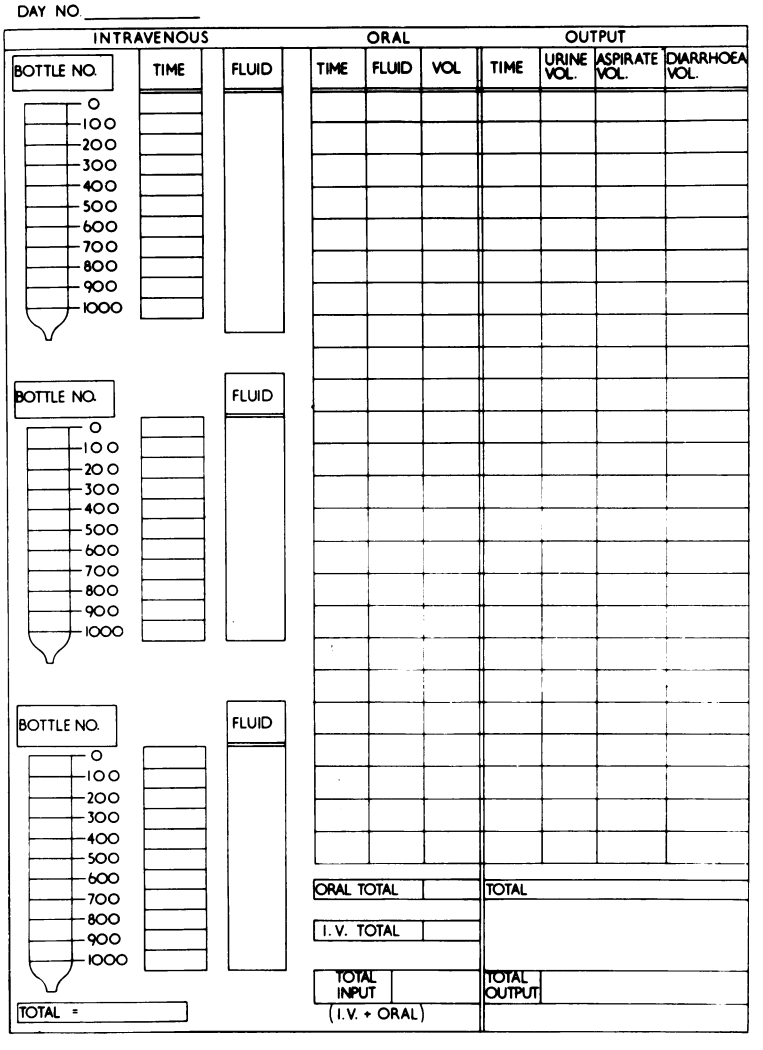

FIG. 1. Chart used for fluid balance data in routine patient management.

The facts concerning the output side of the balance equation are more numerous and no less important. Water losses in the stool and skin may be predicted but when there is diarrhoea or sweating the corrections are necessarily very crude. Electrolyte losses by the same routes are more predictable and relatively small when compared to the urinary losses so that corrections are valid. Nitrogen losses

dry matter in the diet (Mendel & Fine, 1912; Mitchell, 1926) and is slightly greater with liquid diets, than solid diets (Forsyth, Shipman & Plough, 1954), so that the corrections are sufficiently accurate for clinical purposes.

A false picture of the metabolic balance of a factor will arise if there is a change in the size of the body pool for that factor. Nitrogen balance, for

example, will seem falsely positive in the presence of a rising blood urea, or falsely negative if the urea falls. A further correction is needed if the body pool varies in size during the balance study.

In spite of these limitations the extensive use of balance studies over the last 20 years is adequate testimony of its value. The method compares favourably with isotope methods, although the latter give more precise information at any one instant of time, are more rapidly performed and have no cumulative errors (Wilson *et al.*, 1954). Balance measurements, furthermore, can provide a dynamic picture of total metabolic exchanges over any required period of time. The techniques employed by the writer require no elaborate apparatus and can be completely supervised by nursing and junior laboratory staff (Jones & Peaston, 1966).

Some of the earlier results of the method provided basic observations on the metabolic response to injury, and since the observations of Cuthbertson (1930) balance data have been used to study various conditions, some of which are shown in Table 2.

Technique for external metabolic balance

Application of the method requires the collaboration of medical, nursing and laboratory staff. In the studies to be described, urine was collective into 4-litre polyethylene bottles containing about 5 ml of a preservative (Racasan, Ellesmere Port, Cheshire) or a few crystals of thymol. In patients with self-retaining urinary catheters, the urine drained into graduated plastic bags and was transferred at the end of the 'balance day'. The 'balance day' started at 08.00 hours on one day and ended at 08.00 hours the next. The intake, if by naso-gastric tube, was entered in the column (Fig. 1) 'oral intake', and the volume of diet given recorded (for a patient on 3 l/day of liquid diet an aliquot of 125 ml would be given hourly). Intravenous therapy was recorded in the left-hand column of the chart, and the volume of fluid was recorded by marking the appropriate time in the space provided. The procedure was explained to the nursing staff in an instruction sheet.

Urine output was recorded by hourly readings of the volume of urine contained in the plastic bag. Total daily urine volumes were always checked by using graduated glassware.

Laboratory technique. After measurement of total volume and specific gravity, 10-ml samples were taken and kept in stoppered polyethylene tubes. Aliquots from this sample were analysed for sodium, potassium, chloride, total nitrogen, urea and ammonia.

Sodium and potassium were measured by a laboratory-built flame photometer with internal lithium standard. Chloride was measured on an Evans Electroselenium Chloride meter. Total nitrogen was measured by the micro-Kjeldahl method, employing the modifications (Wootton, 1964) of the original Kjeldahl method (Kjeldahl, 1883). Urea was measured on a Technicon AutoAnalyzer (Wootton, 1964), and urinary ammonia by the Conway microdiffusion method (Conway, 1947).

Corrections for non-urinary losses

Corrections were applied for water lost in the stool and from the skin, for variations in blood urea, for electrolyte lost in the stool and sweat, and for nitrogen lost by these routes. As far as possible patients with diarrhoea were excluded from study in view of the considerable nitrogen losses which occur.

In the afebrile subject without diarrhoea or oliguria, and with no abnormal losses as sweat or gastric aspiration, a correction was made for water of 900 ml lost from the skin and lungs per 24 hr and 100 ml from the stool (Randall, 1952; Scribner & Burnell, 1956). A further loss of 500 ml was made for each 1°F of fever (Elkington & Danowski, 1955).

Data for electrolytes lost in insensible perspiration are variable; the range is 0–20 mEq/l for sodium, and similar values are given for potassium and chloride (Bland, 1956; Campbell, Dickinson & Slater, 1960; Conzolazio, Johnson & Pecora, 1963). The electrolyte content of stool is related to the water content (Peters, 1935) and for sodium is normally below 50 mEq/l (Shohl, 1939).

Sodium lost in visible sweat as opposed to insensible perspiration is within the limits of 15–100 mEq/l (Peters & Van Slyke, 1931; Black, 1953; Ahlman *et al.*, 1953; Bland, 1956; Baron, 1957; Conzolazio *et al.*, 1963; Statland, 1963; Taylor, 1965). A mean figure based on these observations was used by the writer and is given in Table 3 with other corrections.

Daily nitrogen losses in the sweat are related to the volume of sweat but bear no clear relationship to the amount of nitrogen in the diet (Bost & Borgstrom, 1926). Normal daily nitrogen losses amount to about 0·3 g (Graham & Poulton, 1912). Stool nitrogen loss depends on several factors, but with formed stools is about 1·3 g/day (Peters & Van Slyke, 1932; Thompson & King, 1959).

Projects studied by the author

The work presented here is primarily concerned with the application of external metabolic balance methods to the day-to-day management of patients with serious illnesses, and to the design of suitable naso-gastric or intravenous feeding schemes which would provide optimum nutrition.

Clearly, for maximum use such methods must be capable of supervision by nursing staff, and require a minimum of laboratory analysis. The criterion of adequate metabolic care was taken as a state of balance for the variables measured; 'a state of balance was accepted when the difference between

the intake and urinary excretion lay within the range of predicted losses from the gut, skin and lungs' (Peaston, 1966b).

Metabolic studies on intragastric feeding

Introduction

Although the use of nutrients given via a catheter into the pharynx or oesophagus dates back to a report by Capivacceus in 1598 of feeding through a hollow tube attached to an animal bladder (His, 1925) it was not until 1776 that this technique was described for the direct transmission of food into the stomach. This procedure was advocated by none other than John Hunter himself in a description of supplementary naso-gastric feeding in patients recovering from drowning (Hunter, 1776). He later achieved total naso-gastric nutrition in a man with paralytic dysphagia. Hunter used the tube 'to inject jellies, eggs beat up with a little water, sugar and milk or wine', and the patient was maintained in this way for 18 days until the ability to swallow returned (Hunter, 1837). Isolated reports since that time advocated similar methods but it was not until 1916 that such procedures were used in the management of specific diseases. Intraduodenal feeding by continuous drip methods was advocated for peptic ulcer (Jones, 1916) and followed by the standard intragastric milk drip (Winkelstein, 1933).

In acute medical or surgical illnesses, or following trauma or burns, adequate nutrition is exceptional. The causes of inadequate food or fluid intake include anorexia, nausea, vomiting, paralytic ileus, traumatic or surgical interference to the upper gastro-intestinal or respiratory tract, pain, severe dyspnoea, or impaired consciousness. In the Intensive Care Unit three main schemes of feeding are in use—oral feeding during illnesses of moderate severity, intragastric feeding in severe illness and intravenous feeding. Because, in desperate illness, adverse changes in the body fluids arise rapidly, no patient is allowed to starve for more than 6 hr.

Apathy, confusion, anorexia or dyspnoea may prevent a patient eating the food needed to maintain metabolic balance. In such patients nutrition depends on their ability to take small frequent nutritious feeds, and the willingness of the nursing staff to encourage the patient to take such feeds. Nonetheless, the hospital 'light diet' provides inadequate nutrition (Davidson & Passmore, 1966) and 'the dietary practices in hospitals have not kept up with recent advances in the field of therapeutic nutrition. The majority of therapeutic diets outlined in hospital manuals do not supply nutrients necessary for good nutrition for acute illness, convalescence and rehabilitation' (Pollack & Halpern, 1952). The nursing encouragement depends on both the individual nurse and the number of nurses on the ward at any one time—in a general ward this is nearly always

TABLE 3

Corrections for daily losses from the lungs, skin and gut

	Water (l.)	Sodium (mEq/l)	Potassium (mEq/l)	Chloride (mEq/l)	Nitrogen (g/l)
Insensible perspiration	0·5	12	10	12	0·6
Lungs	0·4	–	–	–	–
Stool	0·1	40	72	20	13
	Water (l.)	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Nitrogen (g)
Total per day	1·0	10	12	9	1·6
Additional losses from visible sweating per °F					
	Water (l.)	Sodium (mEq/l)	Potassium (mEq/1)	Chloride (mEq/l)	Nitrogen (g/l)
Sweat	0·5	58	10	45	0·3
	Water (l.)	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Nitrogen (g)
Total per °F	0·5	29	5	22	0·15
Correction of nitrogen balance for variations in blood urea					
Per 10 mg change in blood urea per day					±2·3 g

quite inadequate if more than one or two patients require such feeding. If the nurses are available, however, as they are on an Intensive Care Unit, adequate nutrition can be easily supplied by homogenized ward meals and milk feeds (Jones & Peaston, 1966). If this diet is used for external metabolic balance studies, food analysis is required to determine the intake and the laboratory work increases several fold.

Intragastric feeding in severe illness

When feeding by the above scheme is not possible and there are no contra-indications to intragastric feeding, the only adequate route is via a naso-gastric tube. Gastrostomy is unnecessary for illnesses of short duration, and even in a long illness is not essential if nutrition can be preserved by tube feeding. The extensive use of carefully designed tube feeding has satisfied the criteria for adequate nutrition without serious side-effects (Pareira *et al.*, 1954). The method is applicable to intensive patient care (Jones & Sechiari, 1963; Jones & Peaston, 1966; Peaston, 1966c) and to the management of patients with other acute illnesses such as haematemesis from peptic ulcer (Ashby, Anderson & Peaston, 1963).

Design of the experiments

The first external balance studies were made on control subjects given the liquid diet of Jones & Sechiari (1963). It was postulated that if this diet (A) was not adequate to maintain metabolic balance in healthy active controls, it would be inadequate for severely ill patients. The diet A proved to be unsatisfactory and a second diet (B) was designed and tested on controls and patients.

Patients and controls

Seven healthy young adults, aged 25–43 years (five male and two female) received diet A, and seven further normal subjects, aged 16–43 years (four male and three female) received diet B. The modified diet B was next given to twenty patients, aged 25–72 years, admitted to the Intensive Care Unit. Eleven of the patients had severe pulmonary infection and fifteen required IPPV for a mean time of 6·5 days. Thirteen of these cases required tracheostomy. The patients are tabulated in Table 4.

TABLE 4
Tube feeding—the patients

Case	Age (yr)	Sex	Duration of balance (days)	Diagnosis	Duration of IPPV (days)	Tracheostomy	Pulmonary sepsis	Result
1	67	M	9	Haematemesis D.U.	–	–	–	Lived
2	41	M	8	Haematemesis D.U.	–	–	–	Lived
3	65	M	10	Cor pulmonale	8	+	+	Lived
4	55	M	5	Haematemesis D.U.	–	–	–	Lived
5	65	F	10	Bronchopneumonia	10	+	+	Died
6	58	F	9	Radical surgery to head and neck	8	+	–	Lived
7	60	F	4	Pulmonary embolism	4	+	+	Died
8	64	F	11	Pulmonary infarction, polyarteritis nodosa	10	+	+	Lived
9	55	F	5	Status epilepticus	2	–	–	Lived
10	30	F	5	Status asthmaticus	5	+	+	Lived
11	58	M	15	Guillain–Barré syndrome	13	+	+	Lived
12	29	F	6	Mitral stenosis, pulmonary oedema	5	+	–	Died
13	62	F	6	Cor pulmonale	6	+	+	Died
14	66	M	4	Cor pulmonale	4	+	+	Died
15	72	F	4	Bronchopneumonia	4	+	+	Lived
16	68	M	8	Myocardial infarction	3	–	–	Died
17	62	M	10	Muscular dystrophy	7	+	+	Lived
18	71	F	11	Barbiturate poisoning	8	+	+	Lived
19	43	F	12	Diabetic coma, cardiomyopathy	–	–	–	Lived
20	25	M	14	Haematemesis D.U.	–	–	–	Lived

Materials and methods

In diet A 100 g of Complan (Glaxo) and 50 g of lactose were mixed with water to a total volume of 1 litre. The composition of Complan is given in Table 5. Three litres of this mixture were given per 24 hr as hourly aliquots of 125 ml syringed down a naso-gastric tube. The composition of the two feeds is shown in Table 6, and their constituents shown in Table 7. In diet B, the composition was 100 g of

Complan, 100 g of glucose and 3 g of methylcellulose (Celevac) per litre. Since methylcellulose is poorly dispersable in cold water the diet was prepared as follows. The Complan and glucose were mixed in about ½ litre of cold water and the methylcellulose separately dispersed in about 100 ml of boiling water. When fully dispersed the methylcellulose was added and the whole made up to 1 litre. Three litres of this diet were given per 24 hr. To each diet, a few drops of a strong dye (heliotrope) were added to detect any diet entering the lungs of patients with a tracheostomy.

TABLE 5
Composition of Complan per 100 g

Calories	450
Carbohydrate (g)	44
Protein (g)	31
Fat (g)	16
Calcium (mg)	825
Phosphate (mg)	780
Sodium (mg)	400
Potassium (mg)	1100
Chloride (mg)	740
Iron (mg)	8
Iodine (μg)	44
Vitamin A (units)	1100
Vitamin B (mg)	1·2
Riboflavin (mg)	1·1
Nicotinic acid (mg)	7·7
Pantothenic acid (mg)	3·0
Choline (mg)	74
Pyridoxine (mg)	0·4
Vitamin B_{12} (μg)	2·2
Folic acid (μg)	55
Vitamin C (mg)	10
Vitamin D (units)	220
Vitamin E (mg)	5·3
Vitamin K (mg)	1·1

TABLE 6
Composition per litre of the tube feeds

	Diet A	Diet B
Complan (g)	100	100
Lactose (g)	50	–
Glucose (g)	–	100
Methylcellulose (g)	–	3
Sodium (mEq)	–	50*
Chloride (mEq)	–	50*
Water (l.)	*ad* 1·0	*ad* 1·0

* The 50 mEq of NaCl are normally added to only one of the 3 litres of Complan–glucose given per 24 hr.

TABLE 7
Daily constituents of the tube feeds

	Diet A	Diet B
Calories	1950	2580
Water (l.)	2·56	2·56
Nitrogen (g)	14·4	14·4
Carbohydrate (g)	282	432
Fat (g)	48	48
Protein (g)	93	93
Sodium (mEq)	66	116
Potassium (mEq)	84	84
Chloride (mEq)	60	110

Results

On diet A, the controls showed an average weight loss of 0·4 kg (0·87 lb)/day, and negative balance for each factor measured (Table 8). Of these controls, two had severe headache lasting up to 48 hr and a further one had mild headache for 3 days. One subject experienced explosive diarrhoea on returning to a normal diet. These results were considered unsatisfactory. Diarrhoea was also frequently observed in patients given diet A during IPPV. Diet A was therefore shown to be inadequate and required modification because of: incidence of diarrhoea (20%) and a failure to maintain positive nitrogen balance and weight in healthy active adults. Three modifications were therefore made as follows: (1) glucose was exchanged for lactose, (2) the quantity of added sugar was doubled, and (3) methylcellulose was added to provide roughage.

These changes were made on the assumptions that the diarrhoea was due to either lactose intolerance or inadequate roughage, or both, and that the weight loss and negative nitrogen balance was due to either an inadequate calorie supply, or incomplete utilization of lactose or both. It was therefore changed to diet B, and the balance results in controls showed an improved balance picture (Table 8). In the twenty patients studied diet B gave a satisfactory corrected balance for all factors and the negative balances for water and nitrogen were small (Table 8).

Of the twenty patients, seven died (29%) as compared with a total annual mortality in the Unit of 38 in 150 (25%). The mean duration of balance was 8·3 days, as compared with an average duration for all admissions of 6·0 days. Patients fed for shorter periods had less serious illnesses and the shorter duration of external balance was less informative. All the patients presented here had balance data for a minimum of 4 days.

Discussion

The first important problem to solve was that of diarrhoea. With diet A the incidence of this was about 20%. It has been shown that if the diet of small laboratory animals is changed abruptly to one of low roughage content they frequently develop severe intractable diarrhoea (Pitt, 1964, personal communication). A high osmolarity of tube feeds

can cause diarrhoea (Masterton *et al.*, 1963) but this was an unlikely cause because the osmolarity of diet A was not high, and would not explain the absence of diarrhoea with the revised diet which had a greater osmolarity. Lactose intolerance in adults, however, has been increasingly recognized following the discovery of an absent or reduced lactase activity in small-bowel biopsies from patients with lactose-induced diarrhoea (Holzel, Schwartz & Sutcliffe, 1959; Auricchio *et al.*, 1963; Dahlqvist *et al.*, 1963). Subsequently, it has been shown that a considerable proportion of normal adults are intolerant to lactose because of a deficiency of jejunal β-galactosidase which results from prolonged milk or lactose deprivation (Cuatrecases, Lockwood & Caldwell, 1965). This finding has been confirmed by others, who give an incidence of about 35% (Haemmerli *et al.*, 1965; McMichael, Webb & Dawson, 1965), as compared to the 55% found by Cuatrecasas.

of severe trauma or sepsis which were associated with a hypercatabolic state. These patients constitute less than 5% of the admissions to the Intensive Care Unit. Preliminary investigations of this group suggest that it may only be possible to reduce the catabolism in these patients rather than to maintain a metabolic balance.

It is reasonable to deduce from these results that in acute medical illnesses the female requires more than 2000 calories and 10 g of nitrogen and the male not less than 2500 calories and 12 g of nitrogen. Studies on patients fed intravenously substantiate this conclusion. These recommendations do not take into account the increased demands of prior starvation, electrolyte depletion, trauma or invasive sepsis. Although the diet B contains an adequate proportion of essential amino-acids, it was not possible to match the results of Rose. Rose, Eades & Coon (1955) found that in normal adults, a diet containing

TABLE 8

Mean daily balances on the tube feeds

	Diet A		Diet B			
	Controls (7 subjects, 5·0 days)		Controls (7 subjects, 4·6 days)		Patients (20 subjects, 8·3 days)	
	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected	Corrected
Water (l.)	0·4	−0·6	0·79	−0·21	1·18	−0·477
Sodium (mEq)	−17	−27	11	1	66	43
Potassium (mEq)	5	−7	18	6	31	16
Chloride (mEq)	−30	−38	−9	−17	51	32
Nitrogen (g)	−0·61	−2·21	1·07	−0·53	0·94	−0·45
Mean weight loss per day (lb)		0·87		0·05		
Loss of lean muscle mass		66		16		13

In my study, investigation of the cause of the diarrhoea was less important than the design of a diet free from this complication. The modifications were therefore introduced simultaneously instead of consecutively. Since using the diet B the incidence of diarrhoea in patients fed intragastrically during IPPV has fallen from 20% to less than 5%.

The increase in calories was almost certainly responsible for the change in nitrogen balance in the controls and indicated the importance of a generous calorie supply in severe illness. The addition of salt was felt advisable from examination of the sodium balances on diet A. From these control results it is seen that with an intake of sodium of 66 mEq/24 hr, a negative balance for sodium was found, whereas with the addition of an extra 50 mEq/day a state of balance for sodium was found. The results obtained when this diet was given to the patients indicated that it was a satisfactory method of maintaining metabolism, except in cases

the correct proportion of essential amino-acid and sufficient calories would give a positive nitrogen balance on a nitrogen intake as low as 3–5 g/24 hr.

In patients on diet B the small negative nitrogen balance indicated a trivial loss of lean muscle. The satisfactory balances for electrolytes meant that the deficits of sodium or potassium and chloride were corrected.

Metabolic studies on intravenous feeding with fat and amino-acids

In some diseases it may not be possible to maintain metabolism by means of an adequate diet or by tube feeding. The conditions in which intragastric feeding is impossible include vomiting, diarrhoea, ileus, surgical or accidental trauma to the upper gastrointestinal tract, or when the patient must be nursed recumbent.

Conventional intravenous 'feeding' using 2 litres of dextrose or fructose and 1 litre of normal saline

per 24 hr amounts to no more than liquid starvation, supplying no nitrogen and only 400–800 cal/day. When there is invasive sepsis or trauma, the need for early generous feeding is even more important, since in septic starvation 'the body cell mass quickly melts away into a hypotonic ocean of extracellular fluid' (Moore, 1959). The intravenous 'feeding' referred to above tends merely to provide an even larger ocean in which the unfortunate subject is invited to dissolve. Even after uncomplicated cholecystectomy large negative nitrogen balances of 12 g/24 hr are found (Wadstrom & Wiklund, 1964). It has been suggested that the catabolic response to surgery and trauma should not be prevented by the infusion of intravenous protein hydrolysates (Moore & Ball, 1952; Cuthbertson, 1954; Davidson & Passmore, 1966). This idea is probably based on work which suggested that the catabolic response was physiological and a result of adaptation to a high nitrogen turnover (Werner, 1948). It was also claimed that the resulting negative nitrogen balance could not be made positive by an adequate diet (Cuthbertson, 1942). It seems reasonable to point out that a metabolic response to illness or trauma can hardly be 'physiological' since both illness and trauma are pathological. Furthermore it has been admitted that part of the catabolic response was due to a low calorie diet (Werner, 1948) and could be abolished or considerably diminished by the provision of adequate calories and nitrogen (Meyer *et al.*, 1947; Riegel *et al.*, 1947). The catabolic response to surgery depends on the nutritional state of the patient (Peters, 1957) and the diet before operation (Cuthbertson, 1942) and can therefore be modified by treatment. Blood transfusion has been excluded as a contributing factor (Flear & Clarke, 1955; Timoner *et al.*, 1959) and trauma itself is only one of the causes, since non-traumatic illness produces a similar, if smaller, response (Cuthbertson, 1934).

To meet the demands for calories and nitrogen during serious illnesses requiring parenteral nutrition, we have used a fat emulsion and amino-acid solutions.

Fat emulsions

Since fat has a high caloric ratio of 9:1 and does not exert an osmotic pressure, it is theoretically possible to give a large number of calories intravenously in a relatively small fluid volume without causing thrombophlebitis. The need for such a material was emphasized by Moore—'the perfection of intravenous fat emulsions for use in surgical patients has been an objective sought for at least 15 years. It is now a reality' (Moore, 1959). Although the need has been recognized, the difficulty has been to produce an emulsion of small particle size without toxic effects. Extensive studies on fat emulsions derived from cotton-seed and soya bean oils were originally performed on dogs (Collins *et al.*, 1948; Mann *et al.*, 1948; Meng & Freeman, 1948; Meng & Early, 1949; Levine *et al.*, 1957; Wretlind, 1957; Meyer *et al.*, 1957; Edgren, 1960; Singleton *et al.*, 1960; Oro & Wretlind, 1961). Subsequent clinical and balance studies were made on surgical patients (Gorens *et al.*, 1949; Mann *et al.*, 1949; Jordan, Wilson & Stuart, 1956; Abbott *et al.*, 1957; Beal *et al.*, 1957; Becker & Buxbaum, 1957; Bozian *et al.*, 1957; Ellison & Mueller, 1957; Glas & Birkelo, 1957; Krieger *et al.*, 1957; Lehr *et al.*, 1957; Levey *et al.*, 1957; Levine *et al.*, 1957; Mueller, 1957; Smith, 1957; Upjohn, Creditor & Levenson, 1957; Waddell *et al.*, 1957; Preston & Henegar, 1959; Cohn *et al.*, 1960; Hartwig *et al.*, 1961; Lehr *et al.*, 1962; Schuberth & Wretlind, 1962; Brockner, Larsen & Amris, 1964; Freuchen & Ostergaard, 1964; Schuberth, 1964; Wadstrom & Wiklund, 1964).

This work showed that fat emulsions have a nitrogen-sparing effect which can reduce post-operative nitrogen deficits, are utilized for calorie production, improve the patient's general condition and prevent loss of weight.

Intravenous fat emulsions, however, are not devoid of toxic reactions, which may be classified into acute and delayed reactions. The reports of adverse reactions are numerous but the conclusions are varied (Meng, Cress & Youmans, 1956; Becker & Buxbaum, 1957; Ellison & Mueller, 1957; Forbes, 1957; Jordan, 1957; Levey *et al.*, 1957; Levine *et al.*, 1957; Preston *et al.*, 1957; Smith, 1957; Waddell *et al.*, 1957; Watkin, 1957; Thompson, Johnson & Forbes, 1958; Forbes, Allen & Gray, 1959; Kaley, Meng & Bingham, 1959; Hartwig *et al.*, 1961; Oro & Wretlind, 1961; Amris, Brockner & Larsen, 1964; Wretlind, 1964). In general it seems that the original cottonseed oil emulsions caused a much higher incidence of acute toxic reactions than did soya bean oil emulsions, although this was attributed to the preserving agent gossypol (Wretlind, 1964) which is no longer used. By 1957 it was concluded that the improved cottonseed oil emulsions were sufficiently safe for clinical use (*Metabolism*, 1957) and a similar conclusion was reached for a soya bean oil emulsion (Schuberth, 1964).

Amino-acids

Solutions of amino-acids have been available for several years which could provide amino nitrogen intravenously. These solutions are protein hydrolysates (Table 9) or synthesized amino-acids. Numerous studies have shown that these solutions are utilized and the negative nitrogen balance, which is part of the catabolic response to illness or surgery, reduced. In many of these studies concomitant infusions of fat emulsion were given (for references

see previous section on fat emulsions). The reduction in catabolism has been confirmed by several studies (Christensen *et al.*, 1955; Abbott *et al.*, 1957; Peaston, 1966b). Infusions of amino-acids do not cause a significant increase in the excretion of amino nitrogen (Brocard, Akoun & Fabiani, 1964; Peaston, 1966b). The urinary nitrogen output is greater with protein hydrolysates than with plasma infusions (Levine *et al.*, 1957) but this does not mean that plasma is a better source of nitrogen. The suggestion (Christensen *et al.*, 1955) that the simultaneous administration of carbohydrate increases peptide and amino-acid wastage is not supported by an increased urinary nitrogen excretion. The concomitant supply of potassium increases the utilization of nitrogen given intravenously (Frost & Smith, 1953) and again shows that amino-acids are used for tissue repair. The available evidence suggests that intravenous amino-acids are a readily utilized source of nitrogen, and when given with optimal calories, carbohydrate and electrolyte are a satisfactory substitute for dietary protein.

Sugars and alcohol

The necessity for carbohydrate as a source of energy is too obvious to require elaboration. The difficulty with sugar solutions as a calorie source, however, is that the calories are limited by the fluid load if concentrations are kept sufficiently low to avoid thrombophlebitis. Numerous studies have confirmed the protein-sparing effect of sugar solutions and show that fructose is better than glucose (Cori, 1926; Weichselbaum, Elman & Lund, 1950; Miller *et al.*, 1952; Albanese *et al.*, 1952, 1954; Christensen *et al.*, 1954; Forsyth *et al.*, 1955; Michon, Larcan & Vert, 1960). The reasons for using fructose rather than glucose have been well set out by Thoren (1963). Although the metabolic properties of sorbitol were studied some years ago (Todd, Myers & West, 1939; Seeberg, McQuarrie & Secor, 1955) it is only recently that it has received widespread interest as an agent for parenteral nutrition.

The nitrogen-sparing effect of ethanol has been known since the last century (Atwater & Benedict,

TABLE 9

Composition per litre of intravenous solution used

	Calories	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Nitrogen (g)
Aminosol 10%	320	160	–	130	12·8
Aminosol 3·3%, fructose 15% and ethanol 2·5%	875	54	–	46	4·3
Intralipid 20%	2000	–	–	–	–

TABLE 10

Intravenous feeding—the patients

Case	Age (yr)	Sex	Duration of balance (days)	Intravenous diet	Diagnosis
1	64	M	7	A	Oesophageal carcinoma, malnutrition
2	35	M	6		Barbiturate overdose, schizophrenia
3	68	M	3		Radical cancer surgery of head and neck
4	81	M	5		Malnutrition, uraemia
5	79	M	5		Cerebral thrombosis, malnutrition
6	64	M	5		Bronchiectasis, malnutrition
7	68	M	4	B	Radical cancer surgery of head and neck
8	62	M	6		Malnutrition, chronic bronchitis
9	77	M	7		Malnutrition, chronic bronchitis
10	69	M	5		Malnutrition, chronic bronchitis
11	51	M	4		Sarcomatosis, malnutrition
12	32	M	4		Barbiturate overdose, schizophrenia
13	52	F	5	C	Radical cancer surgery of head and neck
14	65	M	5		Malnutrition, chronic bronchitis
15	68	M	5		Malnutrition, osteoporosis and scurvy
16	82	F	4		Oesophageal stricture, malnutrition
17	78	M	6		Malnutrition, ischaemic heart disease
18	66	M	5		Gastric carcinoma, malnutrition

1897). In small concentrations ethanol increases tissue oxygen uptake (Perman, 1962) and carbohydrate, especially fructose (Pletscher, Bernstein & Staub, 1952) increases the oxidation rate of alcohol (Carpenter & Lee, 1937). Hence the use of low concentrations of ethanol helps to supply more calories by the intravenous route.

The value of using a combination of amino-acids, fructose and ethanol as a source of both calories and nitrogen is thus based on the protein-sparing action of the carbohydrates, and the fact that a deficiency in calories exerts not only an increased fat conversion but also catabolism of amino-acids, which are therefore not available to repair the increased breakdown of the lean muscle mass. Furthermore, since all the non-essential amino-acids are glucogenic, they can contribute both to the available peripheral glucose and spare the essential amino-acids for tissue repair. It is therefore rational to give amino-acids and sugar solutions together. This does not increase the total nitrogen excretion but reduces plasma levels of amino-acids and peptides (Christensen *et al.*, 1955), a finding which suggests an improved tissue utilization of the infused amino-acids.

TABLE 11
Composition of the intravenous diets

	Intravenous diet		
	A	B	C
Materials			
Aminosol-fructose-ethanol (l.)	2·0	1·0	1·5
Aminosol 10% (l.)	–	0·5	0·5
Fructose 20% (l.)	0·5	–	–
Intralipid 20% (l.)	0·5	1·5	1·0
Potassium chloride (g)	6	6	6
Composition			
Calories	3130	4035	3472
Water (l.)	3·0	3·0	3·0
Nitrogen (g)	8·5	10·6	12·8
Carbohydrate (g)	400	150	225
Fat (g)	100	300	200
Sodium (mEq)	108	134	161
Potassium (mEq)	78	78	78
Chloride (mEq)	167	186	209

TABLE 12
External balance data on the intravenous diets

Intravenous diet	No. of patients	Mean duration of balance (days)	Mean intake					Mean output					Mean uncorrected balance					Mean corrected balance					Loss of lean muscle mass (g/day)
			H_2O	Na	K	Cl	N_2	H_2O	Na	K	Cl	N_2	H_2O	Na	K	Cl	N_2	H_2O	Na	K	Cl	N_2	
A	6	5·2	3·33	108	72	167	8·5	1·94	85	56	112	9·9	1·39	23	14	55	−1·5	0·39	13	2	47	−2·83	84·9
B	6	5·0	3·30	134	78	186	10·6	1·46	81	54	108	11·5	1·81	53	24	78	−0·9	0·67	39	10	64	−2·54	76·2
C	6	5·0	3·41	161	78	209	12·8	1·82	132	62	161	11·1	1·59	29	16	45	1·68	0·59	19	4	37	0·08	−2·4

Design of an intravenous diet

The materials used for this study were a fat emulsion prepared from soyabean oil, amino-acid

preparations, potassium chloride and vitamins. The fat and amino-acid solutions used are given in Table 9.

Methods

Eighteen patients with a variety of serious illnesses were studied. The criterion of good nutrition was a balance for water, electrolyte and nitrogen. The patients are shown in Table 10. The first diet contained 8·5 g of amino-acid nitrogen, and this was subsequently modified to give larger amounts of nitrogen (Table 11). When the third intravenous diet had been designed, a comparison was made between this diet, the Complan–glucose tube feed, and the intravenous diet given via the naso-gastric tube.

Results

The balance data on the three intravenous diets are shown in Table 12. It can be seen that the first two diets gave a negative corrected nitrogen balance but the third diet (diet C) achieved a small positive nitrogen balance. The results in terms of loss of the lean muscle in grams per day is also given. The comparison between diet C given intravenously or intragastrically and the Complan–glucose diet is shown in Table 13.

From these data it can be concluded that in a variety of serious illnesses it is possible to achieve a state of metabolic balance for nitrogen and electrolyte by an adequate intravenous diet. This conclusion does not apply to patients with severe trauma, sepsis or hypercatabolic renal failure. In severe hypercatabolism, diet C may only halve the nitrogen losses but will still preserve the muscle mass for twice as long as conventional methods of intravenous feeding. The materials used are also capable of reducing catabolism, as shown by the reduction of catabolic urinary nitrogen (Table 13) without an increased total urinary nitrogen. The intravenous diet C compared favourably with the Complan–glucose diet, which has already been shown capable of maintaining metabolic balance during serious illness.

There are three limitations to the use of such materials. These are the high incidence of thrombophlebitis, the high sodium content of the amino-acid solutions, and the high cost. The incidence of thrombophlebitis has been reduced by the simultaneous infusion of fat and amino-acids through a Y-shaped connector. The bottles are given in pairs over 8-hr periods (Table 14). A further improvement was obtained by changing the infusion site every 24–48 hr. The high sodium content of the amino-acid solutions is due to the sodium hydroxide used in manufacture. At the present time we have to add potassium chloride to the infusion. More satisfactory electrolyte concentration would result if three parts of sodium hydroxide to one part of potassium hydroxide were used during manufacture.

TABLE 13

Mean nitrogen excretion (g/day) during intravenous and intragastric feeding

	Nitrogen intake	Total nitrogen output	Nitrogen balance	Non-urea nitrogen	Urea nitrogen	Ammonia nitrogen	Catabolic nitrogen (urea + NH_3)	Catabolic nitrogen (% of total nitrogen)
Diet C given intravenously	12·8	10·9	+1·9	4·8	6·1	1·2	7·3	67
Diet C given intragastrically	12·8	9·9	+2·9	4·2	5·7	1·1	6·8	69
Complan–glucose diet	12·0	9·9	+2·1	2·3	7·6	1·1	8·7	88

TABLE 14

System of infusions with intravenous diet C

	Bottle No.	Infusion
Infused over 8 hr	1	0·5 litres aminosol–fructose–ethanol plus 26 mEq KCl
	2	0·5 litres 20% Intralipid plus 5000 units heparin
Infused over 8 hr	3	0·5 litres aminosol–fructose–ethanol plus 26 mEq KCl
	4	0·5 litres 10% aminosol
Infused over 8 hr	5	0·5 litres aminosol–fructose–ethanol plus 26 mEq KCl
	6	0·5 litres 20% Intralipid plus 5000 units heparin

Alternatively, synthesized amino-acids can be used, with the advantage that the electrolyte needs can be varied for the individual patient. Whichever materials are chosen, however, it is now clear that metabolism can be maintained in serious illnesses by the intravenous route and that venous lavage with weak sugar and salt solutions is no longer justified and cannot be described as parenteral nutrition.

Acid–base balance

Although this paper primarily concerns the uses of metabolic balance, tube feeding and intravenous diets during intensive patient care, it would be a serious omission to exclude a discussion of the influence of the acid–base state on organ function, and how changes in acid–base can be measured and corrected.

Although an awareness that acid–base changes may be associated with many diseases dates into the last century, it is only recently that apparatus suitable for routine clinical use has become available. Before this time a full understanding of the acid–base state had been worked out by the pioneers in this field (Van Slyke & Cullen, 1917; Van Slyke, 1921; Peters *et al.*, 1926). It was soon appreciated that the measurement of three variables was necessary to describe the acid–base state of whole blood (Hasselbalch, 1916; Peters & Van Slyke, 1932) and that large and rapid changes in two variables could be due to a change in the respiratory component (Henderson & Greenberg, 1934). In recent years the work of Astrup and Siggaard-Andersen has clarified the interpretation of acid–base measurements and produced robust and reliable measuring equipment. The variables required are the pH, $Paco_2$ and the base excess or deficit (Siggaard-Andersen, 1964).

Blood pH is best measured with a glass electrode, of which several types have been used. Probably the most satisfactory capillary glass electrode for clinical use is the electrode manufactured by Radiometer, Copenhagen (Siggaard-Andersen *et al.*, 1960). Measurement of $Paco_2$ can be conveniently made with the same apparatus by interpolation after equilibration of the blood with gases of known CO_2 concentration. For this purpose a shaking chamber (Siggaard-Andersen *et al.*, 1960) has now replaced older tonometric or rocking chamber methods (Barcroft, 1934; Laue, 1951; Hall, 1960). Alternatively, electrodes may be used for direct estimation of $Paco_2$ (Severinghaus & Bradley, 1958; Mendel, 1960). From the measurements of pH and $Paco_2$ the base deficit or excess can be estimated from nomograms constructed from experimental determinations (Siggaard-Andersen, 1962).

From the therapeutic standpoint, metabolic acidosis is the important acid–base change which requires early detection, monitoring and prompt correction. Although the effects of acidosis are numerous, the two important susceptible organs are the heart and the kidneys. Acidosis has a direct depressant effect on myocardial function. Although acidosis following cardiac infarction has only recently been observed (MacKenzie *et al.*, 1964) the acidosis which follows circulatory arrest was recognized earlier. It has long been realized that reduced tissue perfusion with hypoxaemia leads to a metabolic acidosis by changing cell respiration from aerobic glycolysis (Bogue, Evans & Gregory, 1939; Huckabee, 1958). Resuscitation from cardiac arrest is more difficult when an acidosis is present (Dodds & Brummitt, 1963), whereas its prior correction assists considerably the resuscitative measures (Ledingham & Norman, 1962; Stewart, Stewart & Gillies, 1962). The prognosis of myocardial infarction is related to the severity of metabolic acidosis (Neaverson, 1966). This in turn may relate to the severity of hypoxaemia, the correction of which is probably essential to improve the prognosis in myocardial infarction with cardiogenic shock (Peaston, 1966a).

The importance of metabolic acidosis in influencing renal function has in the past unfortunately been obscured by the role of the kidney in preserving the acid–base state. The fact that a metabolic acidosis itself seriously alters renal function, and thereby creates a vicious circle by depressing one of the most important mechanisms for its correction, has been overlooked.

The therapy of metabolic acidosis is simple and convenient. An 8·4% solution of sodium bicarbonate contains 1 mEq of bicarbonate per millilitre of solution, and can be given intravenously without causing thrombophlebitis. The number of milliequivalents required to correct a given base deficit can be simply calculated by the equation:

$$\text{Bicarbonate required (mEq)} = 0{\cdot}3 \times \text{Base deficit} \times \text{Body weight (kg)}$$

(Mellemgaard & Astrup, 1960).

There is no advantage in the use of sodium lactate to correct metabolic acidosis, particularly when in some patients there is already a lactic acidaemia (Huckabee, 1961).

From this brief review, two important principles emerge. Firstly, changes in the acid–base state, particularly metabolic acidosis, may significantly influence recovery from serious illnesses. Secondly, it is now a comparatively simple matter to measure and correct such changes.

Conclusions

From the foregoing, I suggest that in order to provide the optimum conditions for recovery from a serious illness, it is necessary to preserve the nutritional and metabolic state as near the normal as possible. Before therapeutic decisions are made, it is necessary to have the maximum information concerning pre-existing deficits (or occasionally, excesses) of water, electrolyte and nitrogen, and to know whether continuing losses are occurring. It is also necessary to know of prior abnormalities in the acid–base status, and how this state changes during the illness. It has been shown that by the use of standardized methods of naso-gastric or parenteral feeding, and external balance data from urinary

measurements, it is a comparatively simple matter to monitor, correct and preserve the metabolic state.

Changes in the acid–base state arise more rapidly than do those of fluid, electrolyte or nitrogen balance, and frequent arterial blood sampling is necessary to control it. The frequency of the estimations depends largely on variations in ventilation rather than on the metabolic state. In many serious illnesses, particularly in respiratory failure due to crushing injuries of the chest, status epilepticus or status asthmaticus, respiratory treatment takes precedence over metabolic care. Equally, however, attempts to ventilate the hypovolaemic subject nearly always lead to systemic hypotension, impaired renal function, and further metabolic problems. The importance of maintaining metabolism and particularly the hydration of such patients has been stressed elsewhere (Ambiavagar *et al.*, 1966; Ambiavagar & Jones, 1967; Riding, 1967). If adequate oxygenation is preserved, then the resultant additional metabolic complications of tissue hypoxia are avoided, and metabolic acidosis is prevented.

Total metabolic care thus depends largely on adequate nutrition, good tissue perfusion and the maintenance of ventilation. If these are maintained at optimum levels, the environment for recovery from a critical illness has been preserved.

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